Stereochemistry in the Ene Reactions of Singlet Oxygen and Triazolinediones with Allylic Alcohols. A Mechanistic Comparison

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The ene reaction of singlet oxygen with (*Z*)-4-methylpent-3-en-2-ol-2,5,5,5-d_4 (**1-OH-d4**) in nonpolar solvents exhibits a 90% threo diastereoselectivity in the adduct derived from the major syn perepoxide intermediate, but also a moderate threo diastereoselectivity in the adduct derived from the minor anti perepoxide. Photooxygenation of 2,4-dimethylpent-3-en-2-ol (**2**) exhibits a significant solvent dependence in the syn/anti methyl stereoselectivity, with nonpolar solvents promoting syn methyl reactivity, while polar solvents promote anti methyl reactivity. These results are in agreement with a steering effect between hydroxyl and singlet oxygen in the rate-determining step of the reaction. *N*-Phenyltriazolinedione addition to the chiral allylic alcohol 4-methylpent-3-en-2-ol (**1-OH**) is highly threo diastereoselective in nonpolar solvents, with a solvent dependent variation in the threo/erythro ene products. On the other hand, the nonfunctionalized chiral alkene 2,4-dimethyl-2-hexene (**1-Et**) exhibits poor diastereoselectivity. Reaction of PTAD with **1-OH-d4** in nonpolar solvents, exhibits a significant threo diastereoselectivity from the syn aziridinium imide intermediate, and a moderate threo diastereoselectivity from the anti intermediate. These results are consonant with a steering effect between the hydroxyl and the electrophile, as proposed in the case of singlet oxygen addition to allylic alcohols **1-OH** and **2**. In contrast to the analogous $^1O_2$ ene reaction, a solvent independent ratio syn/anti ∼ 50/50 was found in the addition of MTAD to **2**. The intermolecular kinetic isotope effect in the reaction of **2** with MTAD ($k_H/k_D = 1.15 \pm 0.02$), is consistent with formation of the intermediate in fast step, indicative that the steering effect during the formation of aziridium imide is not important in the reaction kinetics. This energetic profile is in contrast to triazolinedione addition to the secondary allylic alcohol **1-OH**, where the high threo selectivity and the slight inverse kinetic isotope effect of $k_H/k_D = 0.98 \pm 0.02$ are consonant with the formation of the intermediate in the rate-determining step. An explanation for the increased reactivity of the syn methyl in the addition of MTAD to **2** (∼50%) is offered.

Introduction

The ene reaction of singlet oxygen ($^1O_2$)[1] and triazolinediones (RTAD, R = methyl or phenyl)[2] with alkenes exhibits a fancinating variety of regio- and stereoselectivities. Although both electrophiles react with alkenes through structurally similar intermediates (perepoxide and aziridinium imide or AI, respectively), the degree and the type of stereoselectivities are often different, primarily due to the different activation parameters of the reactions and to the bulkiness of the electrophiles. In the reaction of $^1O_2$ with trisubstituted alkenes[3] and enol ethers,[4] the more reactive side of the olefin is the more substituted (cis effect). Only a few cases of anti "cis effect" selectivity have been reported.[5] A syn preference due to a phenyl-directing effect has been recently recognized in the photooxygenation of β,β-dimethylstyrene.[6] Triazolinediones exhibit Markovnikov type selectivity.[7] With trisubstituted alkenes[8] and β,β-dimethylstyrene[6] a high preference for syn addition to the more-substituted side has also been found.

In their reactions with cis alkenes the major ene products arise from allylic hydrogen abstraction next to the bulkiest group.[9] Furthermore, a geminal selectivity[10] was observed with respect to a bulky alkyl substituent or a functional group at allylic or vinylic position. The degree of selectivity depends solely on the size of the

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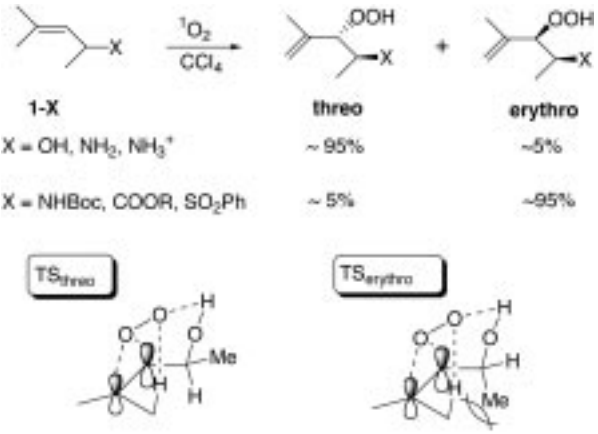
Scheme 1. Diastereoselectivity in the Reaction of $^1O_2$ with Chiral Functionalized Alkenes



electrophile, with triazolinediones affording more highly regioselective reactions. These results were rationalized in terms of nonbonded interactions.[10b,11]

With alkenes bearing an electronwithdrawing group at the β-position a high degree of geminal selectivity has been observed for $^1O_2$ additions,[12] while various selectivities are observed in the few examples studied so far of PTAD addition.[13] It was found from primary and secondary isotope effects that the energy profiles in the ene reactions of the two electrophiles with α,β-unsaturated esters are different.[14] Also, in their reactions with allylsilanes[15] a mechanistic dichotomy occurs, with PTAD giving cis ene products but $^1O_2$ leading to trans products.

Furthermore, in the photooxygenations of chiral alkenes **1-X** (Scheme 1), coordination of $^1O_2$ to hydroxyl[16] or amino[17] functionalities present at the allylic position leads to highly threo diastereoselective ene reactions. Although for **1-X** a diastereoselective reaction would be expected due to the chirality in the adjacent carbon to the double bond, the small difference in steric hindrance[18] (methyl versus hydroxyl or amino group) could not by itself be responsible for the increased diastereomeric excess (>90%). It was suggested that in the intermediate exciplex which has the structural requirements of a perepoxide, oxygen coordinates to hydroxyl (steering effect). The favorable interaction occurs in a transition state which has minimized the 1,3-allylic strain and leads to threo allylic hydroperoxides. In the photooxygenation of electron-poor allylic alcohols,[19] however, the threo selectivity was attributed to stereoelectronic effects, rather to intramolecular hydrogen bonding.

On the other hand, when the allylic substituent does not coordinate to oxygen (e.g., carboxylic acid derivatives, sulfones, halides, etc.)[20] or the reaction favors the formation of the erythro adduct, electronic repulsions between oxygen and functionality were proposed as the factor responsible for that dramatic change in diastereoselectivity. Similarly, oxygen-functionality electronic repulsions were postulated to control the regioselectivity in the photooxygenation of alkenes bearing an electronwithdrawing group at the β-position.[21] A hydroxyl-singlet oxygen steering effect has been also reported to control the π-facial selectivity in the [4 + 2] cycloaddition of $^1O_2$ with chiral naphthyl alcohols[22] and the reaction pathways in the photooxygenation of 1-(alkoxymethyl)-2-aryl-1-*tert*-butyl-2-methoxyethylene.[23]

Although there are many examples of diastereoselective addition of singlet oxygen to alkenes and dienes, there is lack of information concerning the analogous triazolinedione reactions. A few examples have been reported so far in the [4 + 2] cycloaddition of MTAD to chiral dienols[24] and the 2,2-dimethyloxazolidine derivatives of sorbic acid.[25]

In the photooxygenation of substrate **1-OH**, two intermediates, syn and anti, can be formed. There is lack of information about the contribution of each intermediate to the observed diastereoselectivity. We examined the diastereoselectivity resulting from abstraction of allylic hydrogen from the syn and anti methyls of **1-OH** by specific labeling of the syn methyl. Furthermore, to test accurately the validity of the proposed hydroxyl steering effect, we studied the syn/anti methyl reactivity in the photooxygenation of a tertiary allylic alcohol. Since triazolinediones have similar chemical reactivity to singlet oxygen, we also examined for comparison the ene stereoselectivity and diastereoselectivity in the addition of triazolinediones to secondary and tertiary allylic alcohols, and the energy profile of these reactions as well.

Results

Stereoselectivity and Diastereoselectivity in the Ene Reactions of Singlet Oxygen and PTAD with Chiral Secondary Allylic Alcohols. Although the steering effect between hydroxyl and oxygen has been proposed by Adam's group in the photooxygenation of chiral allylic alcohols and amines,[16,17] they postulated that reaction occurs on the more-substituted side of the olefin. To test this hypothesis we examined the diastereoselectivity of the regioselectivity of allylic alcohol

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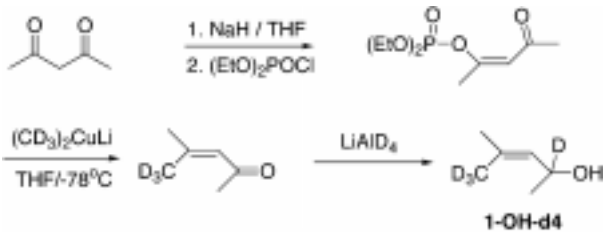
Scheme 2. Preparation of Allylic Alcohol 1-OH-d4



1-OH, by performing the photooxygenation of the selectively labeled allylic alcohol **1-OH-d4**, where the allylic methyl syn to the hydroxyl was selectively labeled as CD_3. Synthesis of **1-OH-d4**, was accomplished by reduction of (*Z*)-4-methylpent-3-en-2-one-5,5,5-d_3, prepared in 94% geometrical purity according to a literature procedure (Scheme 2).[26] To simplify the NMR integrations, the methine hydrogen next to the hydroxyl was labeled as D, by reducing the precursor ketone with $LiAlD_4$.

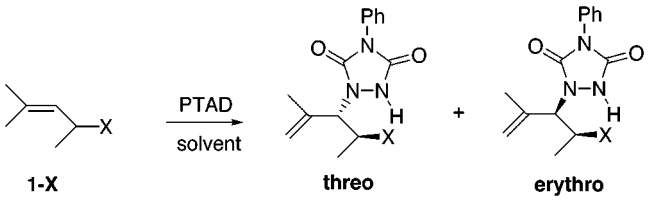
In chloroform the syn/anti methyl reactivity was 84/16 which indicates a "cis effect", as found for nonfunctionalized trisubstituted alkenes.[3] Considering that the reaction proceeds through the formation of a perepoxide as intermediate, we define as syn-perepoxide the intermediate where the oxygen is placed syn to the hydroxyl, and as anti-perepoxide where the oxygen is placed on the less-substituted side of the double bond (anti to the hydroxyl). Integration of the allylic methyl resonances affords the threo/erythro ratio from the syn-perepoxide (D-abstraction), whereas integration of the olefinic protons affords the threo/erythro ratio from the anti-perepoxide (H-abstraction). The diastereoselectivity in the photooxygenation of **1-OH-d4** in choroform is shown in Scheme 3.

The syn-threo/syn-erythro ratio was found to be 77/7 in chloroform, while the anti-threo/anti-erythro ratio was 13/3. When the reaction was run in acetonitrile, the syn/anti methyl reactivity was 82/18, identical within experimental error to that found in chloroform. However, the ratio of diastereomers from each intermediate has changed. The syn-threo/syn-erythro ratio was 63/19, and the anti-threo/anti-erythro 13/5. These results show an increase of the erythro adduct from both the syn and the anti intermediates on going from the nonpolar chloroform to the polar acetonitrile.

To study the stereochemistry of triazolinediones addition to allylic alcohols, we first examined the dependence of the threo/erythro diastereoselectivity on solvent polarity, in the addition of PTAD to the chiral allylic alcohol **1-OH**.[27] The results (Table 1) were compared with the diastereoselectivity observed in the same reaction of the nonfunctionalized chiral alkene **1-Et**, where hydroxyl has been replaced by an ethyl group. The reaction proceeded smoothly at 25 °C without formation of significant byproducts.

The threo/erythro ratios were measured by ^{1}H NMR integration of the appropriate peaks. For **1-Et**, the only well-defined signals were the allylic hydrogens next to the urazole substituent. For **1-OH**, the allylic methyls and the olefinic hydrogens signals are well defined for both isomers in $CDCl_3$ (as NMR solvent). The major

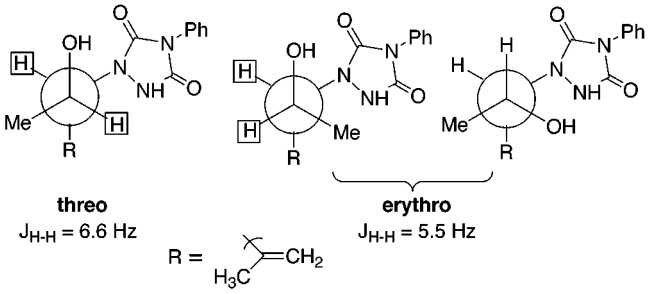
Table 1. Change in the Threo/Erythro Ratio of PTAD Addition to 1-X in Several Solvents



entry	substrate	solvent	threo/erythro
1	1-OH	benzene	91/9
2	1-OH	$CHCl_3$	86/14
3	1-OH	acetone	66/34
4	1-OH	MeOH	62/38
5	1-Et	$CHCl_3$	56/44[a]
6	1-Et	acetone	58/42[a]

[a] The threo/erythro stereochemistry of the two diastereomers was not assigned.

product, tentatively identified from decoupling experiments, was the threo isomer. By irradiating the methyl group doublet (1.24 ppm) at the chiral center which is common for the two diastereomers, the methine hydrogen next to hydroxyl appears as two doublets (at 4.26 ppm, J_1 = 5.5 Hz and at 4.22 ppm with J_2 = 6.6 Hz), corresponding to the two diastereomers in a ratio similar to that measured from integration of the diastereotopic allylic methyls at 1.75 and 1.83 ppm, respectively. The major adduct with the higher coupling constant was assigned the threo structure as one would expect it to have a higher coupling constant than the erythro (see the Newman projections below). The threo diastereomer is represented by the most stable threo rotamer which is expected to have a high coupling constant because of the trans arrangement of the hydrogens. The erythro isomer, whose two more stable rotamers have the hydrogens at gauche to each other, is expected to have a lower coupling constant compared to that of the threo isomer. We consider that in the more stable rotamers, hydroxyl is gauche to the urazole ring due to an intramolecular hydrogen bond.



Similar results in the diastereoselectivity of MTAD addition to several allylic alcohols has been reported independently by Adam and co-workers.[28] The relative configuration of the major adduct was determined to be threo by X-ray analysis of the doubly benzoylated adduct of MTAD with **1-OH**.[29]

To find the syn/anti allylic methyl reactivity in the reaction of **1-OH** and assess further the threo/erythro ratio from the syn- and anti-AI intermediates, the reac-

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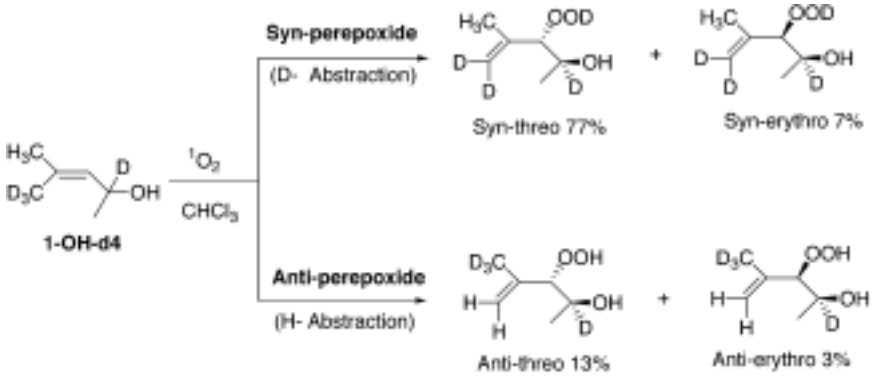
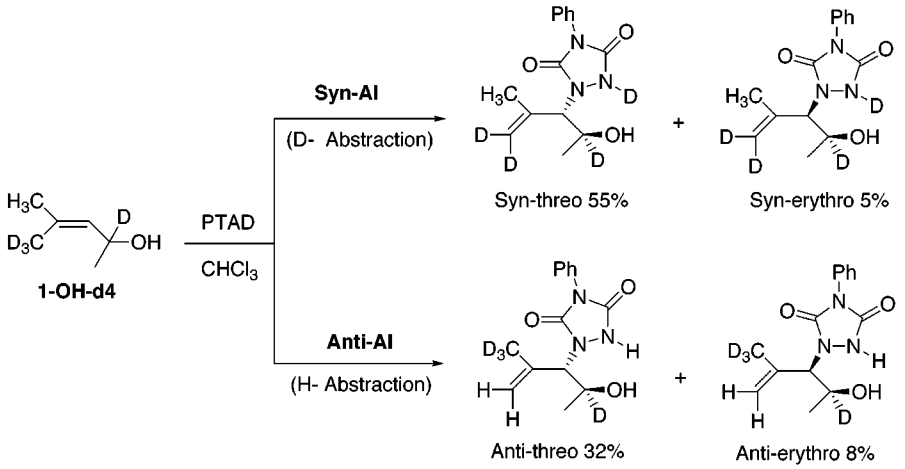
Scheme 3. Products Formed in the Photooxygenation of 1-OH-d4 in Chloroform



Scheme 4. Products Formed by Addition of PTAD to 1-OH-d4 in Chloroform



tion of **1-OH-d4** with PTAD was carried out in chloroform and acetone. The syn/anti methyl reactivity was 60/40 in chloroform and 55/45 in acetone. Considering that the reaction proceeds through the formation of an aziridinium imide as intermediate, we define as syn-AI the intermediate where the PTAD is placed syn to the hydroxyl, and as anti-AI where the PTAD is placed anti. Integration of the allylic methyl resonances affords the threo/erythro ratio from the syn-AI (D-abstraction), and integration of the olefinic protons affords the threo/erythro ratio from the anti-AI (H-abstraction). The diastereoselectivity in chloroform is shown in Scheme 4. When the reaction was run in the more polar acetone, the syn-threo/syn-erythro ratio was 37/18, and the anti-threo/anti-erythro 27/18. As noted in the photooxygenation of **1-OH-d4**, the presence of a D geminal to hydroxyl simplifies the analysis of the adducts in the ^{1}H NMR.

Syn/Anti Methyl Stereoselectivity of a Tertiary Allylic Alcohol with $^1O_2$ and MTAD. To test the validity of the hydroxyl steering effect proposed in the photooxygenation of the secondary alcohol **1-OH**, and to study further the stereochemistry of triazolinedione addition to allylic alcohols, we examined the syn/anti stereoselectivity in the reaction of $^1O_2$ and MTAD with the tertiary allylic alcohol **2**. For this purpose, we synthesized **2Z-d3** and **2E-d3**, respectively, by labeling the syn and the anti methyl group with respect to the functionality. Both electrophiles afford exclusively the ene adducts in quantitative yield. On the more-substituted side of the double bond, oxygen is capable of interacting only with one allylic hydrogen. This experiment eliminates the possibility of having interaction of oxygen with two different allylic hydrogens on the same side of the double bond, as occurs in **1-OH**. Such interaction is well-known to stabilize the transition state for perepoxide formation.[30]

Synthesis of isomeric (*E*)- and (*Z*)-2,4-dimethylpent-3-en-2-ol-5,5,5-d_3 (**2E-d3** and **2Z-d3**), was accomplished through the stereoselective preparation of (*E*)- and (*Z*)-ethyl 3-methylbuten-2-oate-4,4,4-d3, following known literature procedures (Scheme 5).[26,31] Preparation of **2E-d3** was accomplished in 90% geometric purity by the stereoselective addition of $(CD_3)_2CuMgI$ to ethyl tetrolate followed by MeMgI addition to the resulting α,β-unsaturated ester. For the **2Z-d3** isomer, the phosphate ester, derived from deprotonation of ethyl acetoacetate with sodium hydride and subsequent O-alkylation with diethyl chlorophosphate, reacted with $(CD_3)_2CuLi$ to produce in a highly stereoselective manner the ester-d_3, which was then treated with MeMgI to form the desired alcohol in 97% *Z* geometrical purity.

Photooxygenations were carried out at room temperature in the presence of 10^{-3} M 2,6-di-*tert*-butylphenol as a radical scavenger. The xenon Variac Eimac Cermax 300 W lamp was equipped with a filter to cut off the wavelengths below 588 nm. The reaction of allylic alcohols **2E-d3**[32] and **2Z-d3** with $^1O_2$ proceeded smoothly in a variety of solvents to give only the ene products. The

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Scheme 5. Synthesis of 2E-d3 and 2Z-d3

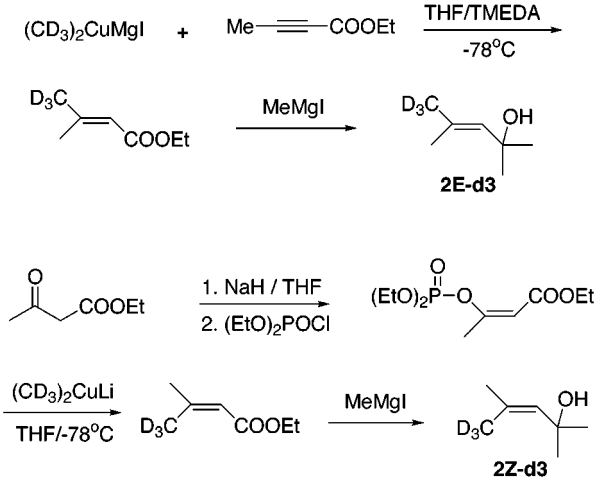
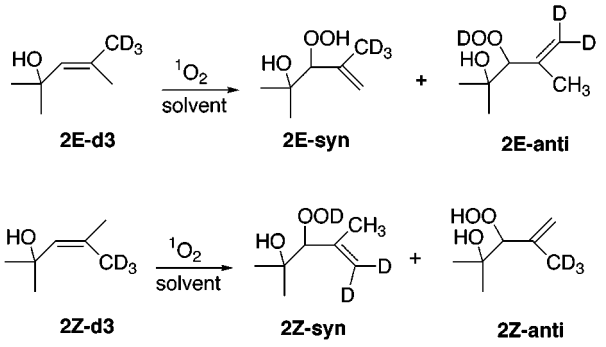


Table 2. Syn/Anti Stereoselectivity in the Photooxygenation of 2E-d3 and 2Z-d3 in a Variety of Solvents



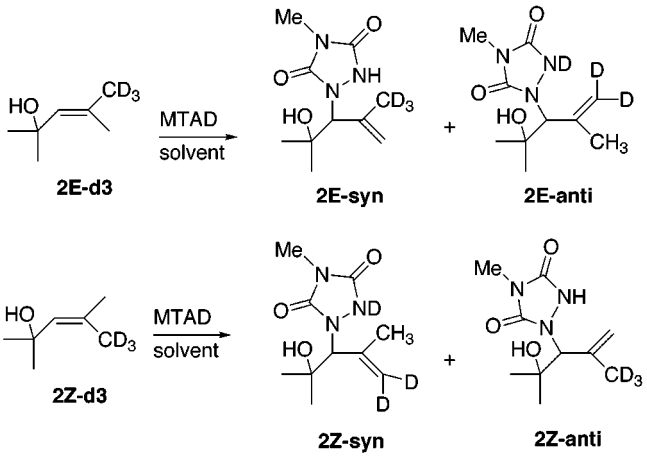
entry	substrate	solvent	sensitizer[a]	syn/anti selectivity
1	**2E-d3**	CCl_4	TPP	75/25
2	**2Z-d3**	CCl_4	TPP	72/28
3	**2E-d3**	benzene	TPP	73/27
4	**2E-d3**	$CHCl_3$	MB	66/34
5	**2Z-d3**	$CHCl_3$	TPP	65/35
6	**2E-d3**	acetone	MB	42/58
7	**2E-d3**	CH_3CN	MB	41/59
8	**2Z-d3**	CH_3CN	RB	40/60
9	**2E-d3**	MeOH	MB	33/67

[a] Abbreviations. TPP: tetraphenylporphine, MB: methylene blue, RB: rose bengal.

product ratio was measured by ^{1}H NMR integration of the appropriate peaks (see Experimental Section). The results are summarized in Table 2. We define as syn the adducts formed by allylic hydrogen abstraction which is on the same side of the double bond as the hydroxyl. For the case of **2E-d3**, the syn adduct is formed by hydrogen abstraction, while for the case of **2Z-d3** by deuterium abstraction. In fact, adducts **2E-syn** and **2Z-anti** are identical, and **2E-anti** and **2Z-syn** are also identical.

Triazolinedione additions were carried out by adding solid MTAD directly into the NMR tube that contained a solution of the allylic alcohols. The product ratio was measured directly by ^{1}H NMR integration of the appropriate peaks (see Experimental Section). When necessary the adducts were purified by flash column chromatography. Reactions of **2E-d3** and **2Z-d3** with MTAD are

Table 3. Syn/Anti Stereoselectivity in the Ene Reaction of 2E-d3 and 2Z-d3 with MTAD in a Variety of Solvents



entry	substrate	solvent	syn/anti selectivity
1	**2E-d3**	benzene-d_6	54/56
2	**2Z-d3**	benzene-d_6	47/53
3	**2E-d3**	$CDCl_3$	56/44
4	**2Z-d3**	$CDCl_3$	45/55
5	**2E-d3**	acetone-d^1	58/42
6	**2Z-d3**	acetone-d^1	44/56
7	**2E-d3**	CD_3CN	55/45
8	**2Z-d3**	CD_3CN	47/53
9	**2E-d3**	MeOH-d_4	55/45

fast, without formation of any significant amounts of byproducts or methoxy adducts[33] in methanol. The definition of **2E-syn**, **2E-anti**, 2Z-syn, and 2Z-anti is the same as that used in the description of the photooxygenation reaction. The surprising result is that the syn/anti stereoselectivity for each isomer is solvent independent (Table 3), in contrast to the $^1O_2$ reactions where the ratio is highly solvent dependent. However, a small change was found on going from **2E-d3** (syn/anti = 55/45) to **2Z-d3** (syn/anti = 45/55).

Intermolecular Kinetic Isotope Effects in the Reaction of MTAD with 1-OH and 2. To elucidate the energy profile of triazolinedione addition to allylic alcohols, we measured the intermolecular kinetic isotope effects in the reaction of MTAD with the chiral secondary allylic alcohol **1-OH** and the tertiary allylic alcohol **2**. For this purpose, we synthesized the deuterated allylic alcohols **1-OH-d10** and **2-d10** according to Scheme 6, through the common precursor, mesityl oxide-d_{10}.

The kinetic competition of **1-OH** versus **1-OH-d10**, and for **2** versus **2-d10** in chloroform, was monitored by GC on a 5% methyl phenyl silicone capillary column, using nonane as an internal standard. The deuterated alkenes have sufficient separation from their perprotio analogues, and their retention times are shorter. The results are depicted in Scheme 6. The observed total isotope effects are almost unity for the reaction of the secondary allylic alcohol **1-OH**, while for the tertiary allylic alcohol **2** a small isotope effect was measured.

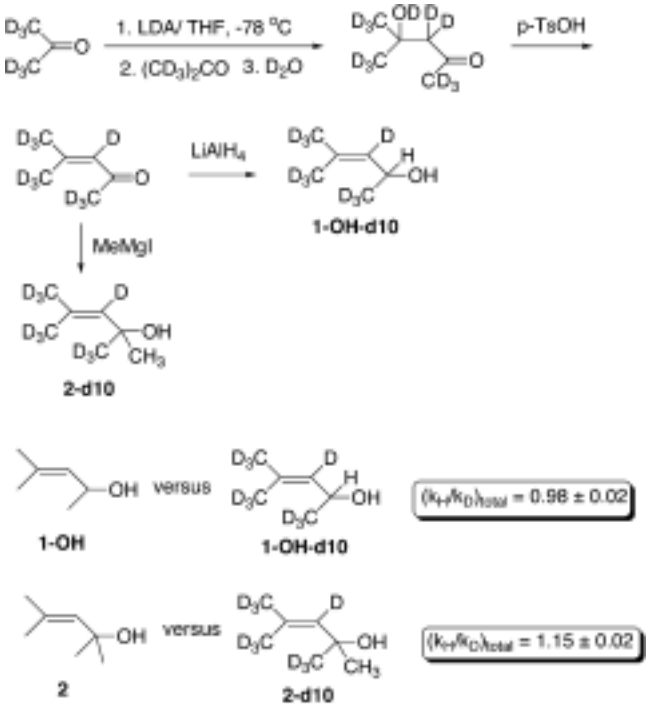
Discussion

(a) Photooxygenation of Secondary Allylic Alcohol 1-OH. We view the reaction as proceeding through the intermediacy of a perepoxide or through an exciplex

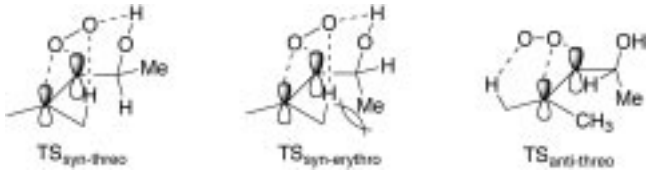
(32) Preliminary results in the photooxygenation of **2E**−**d3** have been communicated earlier: Stratakis, M.; Orfanopoulos, M.; Foote, C. S. *Tetrahedron Lett.* **1996**, *37*, 7159−7162.

(33) Smonou, I.; Khan, S.; Foote, C. S.; Elemes, Y.; Mavridis, I. M.; Pantidou, A.; Orfanopoulos, M. *J. Am. Chem. Soc.* **1995**, *117*, 7081−7087.

Scheme 6. Synthesis of Deuterated Allylic Alcohols 1-OH-d10, 2-d10 and Intermolecular Isotope Effects in Their Ene Reactions with MTAD



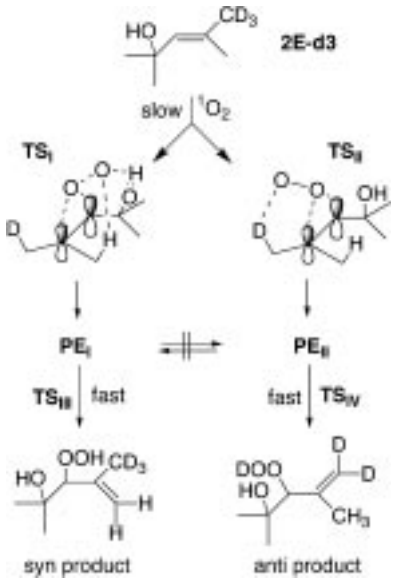
Scheme 7. Possible Transition States in the Photooxygenation of 1-OH



with the structural requirements of a perepoxide. As seen in Scheme 3, in the photooxygenation of **1-OH-d4** in chloroform, the syn-intermediate is formed in 84% ratio and results in a 11/1 threo to erythro diastereoselectivity. On the other hand the anti-intermediate, formed in 16% ratio, also affords threo diastereoselectivity (threo/erythro = 4.3/1), but to a minor extent compared to the syn-intermediate. The diastereoselectivity in the photooxygenation of **1-OH** (threo/erythro = 90/10) is almost identical to that from the syn-intermediate, since this intermediate predominates over the anti-intermediate. For the syn-intermediate, it seems likely that oxygen interacts with hydroxyl in a transition state with the minimum 1,3-allylic strain and directs the reaction diastereoselectivity, as proposed by Adam and co-worker,[16a,b] who also considered the syn-intermediate to be predominant (Scheme 7). For the anti-intermediate, we assume that the threo diastereoselectivity could be attributed to the transition state $TS_{anti-threo}$ in Scheme 7. In that transition state, oxygen approaches the double bond from the face where the least steric repulsions are developing. All other conformations, including those leading to erythro adducts, seem to be less favorable.

In the more polar acetonitrile, there is a decrease in the threo/erythro ratio, from both syn and anti intermediates, which is more significant in the case of the syn-intermediate. For the syn-intermediate, solvation of hydroxyl through hydrogen bonding reduces the favorable oxygen−hydroxyl steering effect. Thus the threo/erythro ratio decreases from 11/1 in chloroform to 3.3/1 in acetonitrile. Also, for the anti-intermediate, the threo/erythro ratio decreases from 4.3/1 in chloroform to 2.6/1 in acetonitrile. This could be attributed to the solvation of hydroxyl group, which increases its bulkiness and reduces the energy difference between $TS_{anti-erythro}$ and $TS_{anti-threo}$.

Scheme 8. Proposed Mechanism in the Photooxygenation of Allylic Alcohol 2E-d3



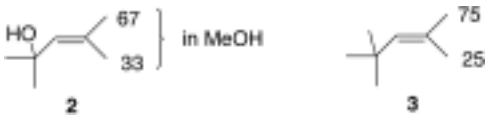
(b) Photooxygenation of Allylic Alcohol 2. We further examined the validity of the oxygen−hydroxyl steering effect by performing the photooxygenation of the tertiary allylic alcohol **2**. Examination of the results in Table 2 reveals that (i) the syn/anti selectivity does not depend on the specific labeling of the methyl groups, which indicates that the rate-determining step of the reaction is the formation of the intermediate as has been found for nonfunctionalized trisubstituted alkenes[34] and (ii) a remarkable difference in the syn/anti methyl reactivity on changing solvent polarity.

In nonpolar solvents a favorable hydroxyl−oxygen interaction during the formation of the perepoxide is very important in stabilizing TS_I where oxygen is syn to the hydroxyl, as seen in the proposed mechanism of the photooxygenation of **2E-d3** (Scheme 8). On the other hand in TS_{II}, no hydroxyl−oxygen steering effect exists and that transition state is higher in energy. The interaction between oxygen and one allylic hydrogen exists in both TS_I and TS_{II}. Thus, the only difference between the two transition states is the stabilizing oxygen−hydroxyl steering effect. The two perepoxides collapse in a faster step through TS_{III} and TS_{IV}, respectively, to the ene products whose ratio reflects the relative stabilities of TS_I and TS_{II}.

In polar solvents, hydroxyl coordinates with the solvent instead of the oxygen. The effective size of −OH becomes large enough for steric hindrance to increase significantly the activation energy of TS_I, thus leading to an almost anti selectivity by favoring TS_{II}. In methanol, for example, the observed syn/anti ratio of 33/67 is approxi-

(34) Stratakis, M.; Orfanopoulos, M.; Chen J. S.; Foote, C. S. *Tetrahedron Lett.* **1996**, *37*, 4105−4108.

mately the same as that observed for 2,4,4-trimethylpent-2-ene (**3**), where a typical anti "cis effect" selectivity syn/anti = 25/75 was observed.[5]



2 **3**

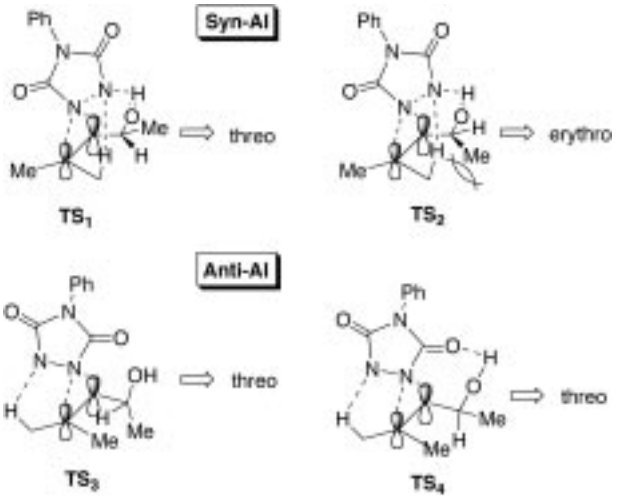
Generally, the regioselectivity of singlet oxygen ene reactions, as measured by the distribution of the ene products, is almost solvent independent. Only in the photooxygenation of α,β-unsaturated esters was a small change in the distribution of the ene products found as a function of solvent polarity, due to the different dipole moments of the two transition states.[35] The current solvent dependence of ene stereoselectivity is the highest ever reported.

(c) Reaction of Triazolinediones with Chiral Secondary Allylic Alcohol 1-OH. The negligible and slight inverse kinetic isotope effect ($k_H/k_D = 0.98 \pm 0.02$) observed in the intermolecular competition of **1-OH** versus **1-OH-d10** clearly rules out the possibility that allylic hydrogen abstraction occurs in a slow step, compared to the preceding transition state of aziridinium imide formation. If we consider formation of AI in the rate-determining step, significant inverse α- and β-secondary isotope effects would be expected[6,36] essentialy due to the rehybridization of the olefinic carbons from sp^2 to sp^3. It rather seems that in the addition of PTAD to **1-OH**, the transition states of the two reaction steps are close in energy, with formation of AI probably being slightly higher. In that case, the inverse isotope effect in the first step and the primary isotope effect of the second step cancel.

We can explain the solvent dependent diastereoselectivity observed in the reaction of **1-OH** with PTAD, considering the possible diastereomeric transition states of AI formation. The contribution of each intermediate (syn and anti) to the total observed diastereoselectivity was measured in the reaction of **1-OH-d4** with PTAD. The threo/erythro selectivity measured from the syn-AI when the reaction was carried out in nonpolar chloroform was 55/5. We consider that, during the formation of the syn-AI, the negatively charged nitrogen of PTAD interacts with hydroxyl in a favorable six-membered ring transition state where the 1,3-allylic strain between the syn allylic methyl and the chiral carbon substituents is minimized (Scheme 9). The transition state where hydrogen interacts sterically with the syn methyl (TS_1) is far more stable than the diastereomeric TS_2, where two methyl groups interact.

The threo selectivity observed from the anti-AI intermediate (threo/erythro = 32/8) can be rationalized in a similar way to the explanation offered for the threo selectivity found from the anti-perepoxide intermediate in the photooxygenation of **1-OH-d4**. The most favorable transition state leading to threo adduct is probably TS_3, in which PTAD attacks the double bond in a conformation where the least steric repulsions are developing. An alternative threo-product transition state (TS_4) where OH is perpendicular to the olefinic plane

Scheme 9. Possible Transition States in the Reaction of 1-OH with PTAD



cannot be ruled out. In TS_4 a steering effect occurs between the carbonyl functionality of PTAD and the hydroxyl in a seven-membered ring transition state. A similar stabilizing interaction between the carbonyl group of PTAD and the silicon has been proposed to be responsible for the observed cis stereochemistry in the ene products derived from PTAD addition to allylsilanes.[15b] However, the stability of transition state TS_4 is questioned, since electronic repulsions between the carbonyl group of MTAD and the oxygen of hydroxyl may also develop. In polar solvents such as acetone, hydrogen bonding between the solvent and the hydroxyl reduces steering efficiency, thus leading to significant amounts of the erythro adducts, as found the analogous $^1O_2$ reaction.

The high efficiency of hydroxyl in controlling the diastereoselectivity of the ene reaction through the steering effect with the electrophile can also be supported by the low diastereoselectivity observed in the reaction of **1-Et** with PTAD (~14% de). This result indicates that steric reasons are less important for the high diastereoselectivity observed in the reaction of **1-OH** with PTAD. We could predict that steric factors could not lead to more than 15% diastereomeric excess in the reaction of PTAD with chiral allylic alcohol **1-OH**, instead of the greater than 80% observed in nonpolar solvents.

(d) Reaction of Triazolinediones with Tertiary Allylic Alcohol 2. The significant results from the reaction of MTAD with the tertiary allylic alcohols **2E-d3** and **2Z-d3** (Table 3), are the following: (i) lack of solvent effect on the syn/anti stereoselectivity; (ii) the unexpected high reactivity of the syn methyl group despite the remarkable steric hindrance, and (iii) a small intermolecular kinetic isotope effect of $k_H/k_D = 1.15 \pm 0.02$ as measured from the direct competition of **2** with **2-d10**.

The lack of solvent dependence in the syn/anti distribution of the ene products is consonant with AI formation occurring in a fast step comparing to the accompanying step of hydrogen abstraction which is the rate-determining. If formation of AI occurred in the rate-determining step, a significant change in the syn/anti allylic methyl reactivity would be expected when changing the solvent, as was observed in the corresponding reaction with singlet oxygen. The normal kinetic intermolecular isotope

(35) Orfanopoulos, M.; Stratakis, M. *Tetrahedron Lett.* **1991**, *49*, 7321−7324.

(36) Elemes, Y.; Orfanopoulos, M. Unpublished results.

effect of $k_H/k_D = 1.15 \pm 0.02$ on competition of **2** versus **2-d10** is consistent with this assumption. Furthermore, the small ratio change from the average syn/anti = 55/45 in **2E-d3** to an average syn/anti = 45/55 in **2Z-d3** is in accordance with the intermolecular competition experiment (**2** versus **2-d10**). An approximate value of $k_H/k_D = 1.2$ can be deduced, considering that in unlabeled olefin, the syn and anti methyls are equally reactive (50/50). If formation of AI occurred in the rate-determining step, a significant inverse isotope secondary effect would be expected. The fact that the isotope effect is normal, but rather small, probably indicates that the hydrogen abstraction is rate-determining, but its energy is close to the preceding step of AI formation. Similarly, a small value of $k_H/k_D = 1.25$ measured in the reaction of PTAD with *trans*-2-butene was explained in terms of a reversible formation of the AI intermediate.[2c] The surprising fact is that an extra methyl group at the allylic position on going from **1-OH** to **2** can alter the kinetic profile of the reaction with triazolinediones.

The unexpectedly high syn methyl reactivity in the reaction of **2** with triazolinediones (~50%), could be explained as follows. Although the electrophile probably prefers to form the anti-intermediate due to steric reasons, the small percentage of the syn-intermediate is competitive with the anti-intermediate in the accompanying rate-determining step of the reaction, because the allylic hydrogen abstraction from the syn-AI results in significant relief of the steric interactions, not only between the bulky electrophile and the alkene, but also between the cis substituents of the olefin (methyl and dimethylhydroxyl). In other words, the ratio of the formation of the syn-AI/anti-AI does not reflect the ratio of the syn/anti products.

Conclusions

As a mechanistic comparison we found that for both electrophiles ($^1O_2$ and triazolinediones) behave via similar manner in their ene reactions with secondary allylic alcohols. The steering effect between hydroxyl and the electrophiles is significant in the distribution of the diastereomeric ene products. Polar solvents with hydrogen bonding ability minimize this interaction, and hydroxyl behaves sterically almost like a methyl group. For the tertiary allylic alcohols, however, there is a discrepancy in the stereoselectivity of the ene reactions, due to the fact that the two electrophiles have different energetic profiles. For $^1O_2$, a solvent dependent steering effect was observed, because formation of perepoxide occurs in the rate-determining step, whereas for triazolinediones, the absence of a steering effect is consonant with formation of the aziridinium imide in a fast step. The proposed change of the energy profile in the ene reactions of triazolinediones on going from the secondary allylic alcohol **1-OH** to the tertiary **2** was supported by intermolecular kinetic isotope effects.

Experimental Section

Nuclear magnetic resonance spectra were obtained on 250, 360, and 500 MHz instruments. The spectra reported herein were taken in $CDCl_3$. Isomeric purities were determined by NMR and by GC-MS on an HP-5 cross-linked capillary column (5% phenyl methyl silicone) equipped with a 5971A MS detector. Diethyl ether, diglyme, and THF were distilled from Na/benzophenone. *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and diisopropylamine were refluxed for 24 h with $LiAlH_4$ and then distilled and kept over 3 Å molecular sieves.

4-Methylpent-3-en-2-ol (1-OH). The compound was prepared by MeMgI addition to 3-methyl-2-butenal at 0 °C, or by reduction of mesityl oxide with $LiAlH_4$, and was purified by vaccum distillation. ^{1}H NMR: 5.21 (d with allylic couplings, $J_1 = 8.6$ Hz, $J_2 = 1.1$ Hz, $J_3 = 1.0$ Hz, 1H), 4.56 (m, 1H), 1.71 (d, $J = 1.0$ Hz, 3H), 1.69 (d, $J = 1.1$ Hz, 3H), 1.40 (br s, 1H, hydroxyl), 1.23 (d, $J = 6.3$ Hz, 3H).

Adducts from 1-OH and 4-Phenyl-1,2,4-triazoline-3,5-dione. The ene products were obtained by adding solid PTAD to a solution of **1-OH** in several solvents and were purified by flash column chromatography using ethyl acetate as eluent (the diastereomers elute together). ^{1}H NMR: 7.35−7.50 (m, 5H threo + 5H erythro), 5.12 (d, $J = 1.4$ Hz, 1H erythro), 5.10 (s, 1H, erythro), 5.07 (s, 1H threo), 5.04 (s, 1H threo), 4.20−4.37 (m, 2H threo + 2H erythro), 1.83 (s, 3H erythro), 1.75 (s, 3H threo), 1.24 (d, $J = 6.1$ Hz, 3H threo + 3H erythro). MS, $m/z = 275$ (M^+, 5).

(*Z*)-4-Methylpent-3-en-2-one-5,5,5-*d*$_3$. To a slurry containing 1.32 g of NaH (60% in oil) in dry ether was slowly added at 0 °C 3 g of acetylacetone (30 mmol). After stirring for 20 min, 5.7 g of diethyl chlorophosphate (33 mmol) was added. Stirring was continued for an additional 2 h, and then the solution was quenched with saturated solution of NH_4Cl and extracted with ether to afford 7.3 g of enol phosphate (89% yield). ^{1}H NMR: 5.44 (s, 1H), 4.20 (m, 4H), 2.26 (s, 3H), 2.15 (s, 3H), 1.33 (dt, $J_{H-H} = 7.1$ Hz, $J_{H-P} = 1.1$ Hz, 6H). Subsequently, the enol phosphate was slowly added to a solution containing 53.8 equiv (26.9 mmol) of $(CD_3)_2CuLi$ at −78 °C. The $(CD_3)_2CuLi$ was prepared by addition of 53.8 mmol of CD_3Li (from CD_3I and Li in ether) to 26.9 mmol of CuI at 0 °C. The solution was stirred at −78 °C for 4 h and then quenched with a saturated solution of NH_4Cl. The ether layer was washed with 25% aqueous NH_3 and then with brine. The mesityl oxide-d_3 was isolated after distillation in 62% yield (1.70 g). The isomeric purity was 95%. ^{1}H NMR: 6.07 (d, $J = 1.2$ Hz, 1H), 2.14 (s, 3H), 1.86 (d, $J = 1.2$ Hz, 3H). MS, $m/z = 101$ (M^+, 50).

(*Z*)-4-Methylpent-3-en-2-ol-2,5,5,5-*d*$_4$ (1-OH-d4). The (*Z*)-4-Methylpent-3-en-2-one-5,5,5-d3 (1.7 g, 16.8 mmol) was reduced with $LiAlD_4$ (0.53 g, 12.6 mmol) in ether, to form the allylic alcohol **1-OH-d4** in 74% yield. The geometric purity of the olefin was 94%. ^{1}H NMR: 5.20 (br s, 1H), 1.70 (d, $J = 1.3$ Hz, 3H), 1.21 (s, 3H). MS, $m/z = 104$ (M^+, 15).

Photooxygenation of 1-OH-d4. The ^{1}H NMR data for the products in the photooxidation of **1-OH** have been reported by Adam and co-workers.[16b] The product ratio of syn-threo/syn-erythro can be found by integrating the allylic hydrogens resonating at 1.73 and 1.80 ppm, respectively. The product ratio of anti-threo/anti-erythro can be found by integrating the olefinic region (5.07 ppm 1 H threo + 1H erythro, 5.09 ppm 1H threo, and at 5.12 ppm 1H erythro).

Addition of PTAD to 1-OH-d4. The product analysis was accomplished by direct NMR integration of the appropriate peaks in chloroform-*d* or acetone-d_6. The product ratio of syn-threo/syn-erythro can be found by integrating the allylic hydrogens resonating at 1.75 and 1.83 ppm, respectively. The product ratio of anti-threo/anti-erythro can be found by integrating the olefinic region (5.04 ppm 1 H threo, 5.07 ppm 1H threo, 5.10 ppm 1H erythro, 5.12 ppm 1H erythro).

2,4-Dimethylhex-2-ene (1-Et). This compound was prepared by Wittig coupling of isopropylidenetriphenylphosponium ylide with 2-methylbutyraldehyde. The ylide was prepared by deprotonation of isopropyltriphenylphosphonium bromide in dry diglyme using NaH as base, at 110 °C for 2 h. The olefin was distilled out from the reaction mixture by a slow stream of nitrogen and then purified by preparative GC (SE-30, Tcolumn = 60 °C). ^{1}H NMR: 4.87 (d with allylic

coupling, $J_1 = 8.0$ Hz, $J_2 = 1.1$ Hz, 1H), 2.20 (m, 1H), 1.68 (d, $J = 1.1$ Hz, 3H), 1.60 (d, $J = 1.1$ Hz, 3H), 0.79−0.98 (m, 8H).

Reaction of 1-Et with PTAD. Two diastereomers were formed in chloroform (56/44 ratio) and in acetone (58/42 ratio). The stereochemistry of each isomer (which is threo and which is erythro) was not assigned. ^{1}H NMR: 7.37−7.55 (m, 5H threo + 5H erythro), 5.07 (br s, 2H threo + 2H erythro), 4.31 (d, $J = 10.8$ Hz, 1H of the major diastereomer), 4.27 (d, $J = 11.0$ Hz, 1H of the minor diastereomer), 2.04 (m, 1H threo + 1H erythro), 1.81 (s, 3H threo + 3H erythro), 1.51 (m, 1H threo + 1H erythro), 1.01−1.24 (m, 1H threo + 1H erythro), 0.91 (m, 6H threo + 6H erythro).

(*E*)-Ethyl 3-Methylbut-2-enoate-4,4,4-*d*$_3$. To a flame-dried flask containing 1.14 g (60 mmol) of CuI in 100 mL of dry THF was added dropwise at −40 °C 55 mL of CD_3MgI (1.0 M in ether, Aldrich). After 30 min, 22 mL of dry TMEDA was added. The solution was cooled to −78 °C, and then 2.3 mL (20 mmol) of ethyl tetrolate was syringed in. After 6 h the reaction mixture was quenched with 8 mL of methanol and 4 mL of saturated solution of NH_4Cl. GC analysis showed approximately 1.5% of starting material present. The α,β-unsaturated ester-d_3 (1.8 g, 69% yield) was a mixture of E/Z = 90/10. It is crucial to maintain the reaction temperature at −78 °C; otherwise, the amount of the Z isomer increases significantly. ^{1}H NMR of the major isomer (E): 5.67 (d, $J =$ 1.1 Hz, 1H), 4.14 (q, $J = 7.2$ Hz, 2H), 2.16 (d, $J = 1.1$ Hz, 3H), 1.27 (t, $J = 7.2$ Hz, 3H).

(*E*)-2,4-Dimethylpent-3-en-2-ol-5,5,5-*d*$_3$ (2E-d3). A solution of the above ester in dry ether was added dropwise at 0 °C to 2.5 equiv of MeMgI. After stirring at ambient temperature for 5 h, the reaction was quenched with saturated solution of NH_4Cl and immediately transferred to a separating funnel, where 1−2 mL of pyridine were added, and the organic layer was washed with saturated solution of $NaHCO_3$ and brine. Removal of the ether left approximately a 1:1 mixture of **2E-d3** and pyridine. Further purification was achieved by vacuum distillation in the presence of solid K_2CO_3. In the absence of pyridine the labile[37] tertiary allylic alcohol dehydrates on standing. The geometrical purity was 90%. ^{1}H NMR of the major isomer (E): 5.33 (d, $J = 1.2$ Hz, 1H), 1.85 (d, $J = 1.2$ Hz, 3H), 1.60 (br s, 1H, hydroxyl), 1.35 (s, 6H). ^{13}C NMR: 17.8, 25.8 (septet due to the D coupling), 30.4, 69.5, 131.9, 132.1. HRMS: calculated for $C_7D_3H_{11}O$ 117.1233, found 117.1234.

(*Z*)-Ethyl 3-Methylbut-2-enoate-4,4,4-*d*$_3$. To a dry flask containing 60 mL dry THF and 1.28 g (32 mmol) of NaH (60% in oil) were added dropwise 3.9 g (30 mmol) of ethyl acetoacetate at 25 °C. Immediate hydrogen evolution occurred. After 20 min, 5.5 g (32 mmol) of diethyl chlorophosphate was added, and the resulting mixture was stirred for an additional 2 h. The reaction mixture was quenched with aqueous NH_4Cl, extracted with ether, and washed with saturated solution of $NaHCO_3$, to afford the enol phosphate in 88% yield. ^{1}H NMR: 5.26 (s with allylic coupling, $J = 1.0$ Hz, 1H), 4.22 (m, 4H), 4.10 (q, $J = 7.1$ Hz, 2H), 2.12 (d, $J = 1.0$ Hz, 3H), 1.32 (dt, $J_1 = 7.1$ Hz, $J_2 = 1.1$ Hz, 6H), 1.21 (t, $J = 7.1$ Hz, 3H). Subsequently, 7.5 g (26.5 mmol) of the above enol phosphate was added dropwise at −78 °C to a solution of $(CD_3)_2CuLi$ (26.5 mmol). The dimethyl-d_6 cuprate was prepared by addition of 2 equiv of CD_3Li to 1 equiv of CuI in dry ether at 0 °C. The resulting mixture was stirred at low temperature for an additional 4 h and then quenched with a saturated solution of NH_4Cl and extracted with ether. The organic layer was washed with 25% aqueous NH_3 and brine. Distillation afforded 1.86 g of pure ester (54% yield) in 97% Z geometrical purity. ^{1}H NMR: 5.67 (d, $J = 1.2$ Hz, 1H), 4.14 (q, $J = 7.2$ Hz, 2H), 1.89 (d, $J = 1.2$ Hz, 3H), 1.27 (t, $J = 7.2$ Hz, 3H). MS, m/z = 131 (M^+, 40).

(*Z*)-2,4-Dimethylpent-3-en-2-ol-5,5,5-*d*$_3$ (2Z-d3). This compound was produced in a similar way to **2E-d3**, by reacting the (Z)-ethyl 3-methylbuten-2-oate-4,4,4-d_3 with 2.5 equiv of MeMgI in ether in 80% yield and 97% geometrical purity. ^{1}H NMR: 5.33 (d, $J = 1.3$ Hz, 1H), 1.69 (d, $J = 1.3$ Hz, 3H), 1.55 (br s, 1H, hydroxyl), 1.35 (s, 6H). ^{13}C NMR: 17.5 (septet due to the D coupling), 26.7, 30.9, 70.1, 132.2, 132.9.

Photooxygenation of 2E-d3 and 2Z-d3. Photooxidation of **2E-d3** in several solvents afforded two ene products, **2E-syn** and **2E-anti**. Their ratio was measured by integration of the appropriate peaks. In the photooxygenation of **2E-d3** the ^{1}H NMR is as follows: 5.15 (d, $J = 1.7$ Hz, 1H of **2E-syn**), 5.07 (d, $J = 1.1$ Hz, 1H of **2E-syn**), 4.27 (s, 1H of **2E-syn** and 1H of **2E-anti**), 1.86 (s, 3H of **2E-anti**), 1.24 (s, 3H of **2E-syn** and 3H of **2E-anti**), 1.22 (s, 3H of **2E-syn** and 3H of **2E-anti**). In the photooxygenation of **2Z-d3** the product analysis occurs in a similar way.

Reaction of 2E-d3 and 2Z-d3 with MTAD. Reaction of **2E-d3** with MTAD in several solvents afforded two ene products, **2E-syn** and **2E-anti**. Their ratio was measured by integration of the appropriate peaks. In the reaction of MTAD with **2E-d3** the ^{1}H NMR is as follows: 5.16 (d, $J = 1.4$ Hz, 1H of **2E-syn**), 5.07 (d, $J = 1.5$ Hz, 1H of **2E-syn**), 4.36 (s, 1H of **2E-syn** and 1H of **2E-anti**), 3.09 (s, 3H of **2E-syn** and 3H of **2E-anti**), 1.90 (s, 3H of **2E-anti**), 1.36 (s, 3H of **2E-syn** and 3H of **2E-anti**), 1.33 (s, 3H of **2E-syn** and 3H of **2E-anti**). In the reaction of MTAD with **2Z-d3** the product analysis occurs in a similar way.

4-Methylpent-3-en-2-one-*d*$_{10}$ (mesityl oxide-*d*$_{10}$). To a dry flask containing 3 g (30 mmol) of diisopropylamine in 15 mL of dry THF was added at 0 °C 18.8 mL of n-BuLi (1.6 M in hexane). The solution was cooled to −78 °C, and then 1.90 g (30 mmol) of acetone-d_6 were slowly syringed in. After 1 h, the enolate reacted with 1.90 g (30 mmol) of acetone-d_6. Stirring was continued for 2 h, and then the solution was warmed to room temperature and quenched with 1.5 mL of saturated solution of NH_4Cl (in D_2O). The aldol adduct was isolated by extraction with ether and was dehydrated neat, on heating with a catalytic amount of p-toluenesulfonic acid. The deuterated mesityl oxide was isolated by vacuum distillation in 40% overall yield (1.3 g).

4-Methylpent-3-en-2-ol-1,1,1,3,5,5,5,4′,4′,4′-*d*$_{10}$ (1-OH-d$_{10}$). The mesityl oxide-d_{10} was reduced by $LiAlH_4$ in ether to afford 4-methylpent-3-en-2-ol-1,1,1,3,5,5,5,4′,4′,4′-d_{10} in 72% yield. ^{1}H NMR: 4.56 (s, 1H), 1.50 (br s, 1H, hydroxyl). The deuterium content at the vinylic position was 88%, and at the allylic positions 93%. The H/D scrambling occurred during the acid-catalyzed dehydration of the aldol. MS, m/z=110 (M^+, 5).

Intermolecular Competition of 1-OH versus 1-OH-d10 in the Reaction with MTAD. Perprotio olefin **1-OH** and deuterated olefin **1-OH-d10** have sufficient separation on GC to allow analysis, and the change in the ratio **1-OH**/**1-OH-d10** was easily monitored at several percentages of reaction progress (20−30% conversion). Nonane was used as an internal standard. For the estimation of the kinetic isotope effect the following expression[38] was used:

$$\frac{k_H}{k_D} = \frac{\log[1 - H_r/H_t]}{\log[1 - D_r/D_t]}$$

where H_r and D_r are the amounts of **1-OH** and **1-OH-d10** that reacted, or by analogy, the amounts of adducts formed from **1-OH** and **1-OH-d10**, and H_t and D_t are the initial amounts of **1-OH** and **1-OH-d10**, respectively.

2,4-Dimethylpent-3-en-2-ol-1,1,1,3,5,5,5,4′,4′,4′-*d*$_{10}$ (2-d10). This compound was prepared by MeMgI to 4-methylpent-3-en-2-one-d_{10} in ether. The isolation of the product was

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accomplished following the experimental details in the preparation of **2E-d3** or **2Z-d3**. ^{1}H NMR: 1.50 (br s, 1H, hydroxyl), 1.35 (s, 3H). The H/D scrambling found in the synthesis of **2-d10** is the same found in the synthesis of **1-OH-d10**. MS, m/z = 124 (M^+, 10).

Intermolecular Competition of 2 versus 2-d10 in the Reaction with MTAD. Identical procedure to that used in the intermolecular competition of **1-OH** versus **1-OH-d10** were followed.

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Supporting Information Available: Copies of 29 ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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